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Chemotherapy Is a Safe and Effective Initial Therapy for Infected Malignant Breast and Chest Wall Ulcers

SERGE DAUPHIN, MD,[1] STEVEN KATZ, MD,[1] MAHMOUD EL TAMER, MD,[2] RICHARD WAIT, MD, PhD,[3] CHUL SOHN, MD,[3] AND ALBERT S. BRAVERMAN, MD[1]*

[1]*Division of Hematology-Oncology, Department of Medicine, Health Sciences Center at Brooklyn, State University of New York, Brooklyn, New York*

[2]*Division of Hematology-Oncology, Department of Surgery, Health Sciences Center at Brooklyn, State University of New York, Brooklyn, New York*

[3]*Division of Hematology-Oncology, Department of Radiation Oncology, Health Sciences Center at Brooklyn, State University of New York, Brooklyn, New York*

Background and Objectives: Locally advanced breast cancers may form large, infected skin ulcers, which were traditionally treated with radiation therapy. Neoadjuvant chemotherapy is now standard treatment for locally advanced breast cancer.

Methods: The response of 33 patients with ulcerated breast cancer to primary chemotherapy was retrospectively analyzed. Antibiotics were not used in primary treatment. Tumor and ulcer responses were evaluated independently.

Results: Chemotherapy alone healed 18 of these ulcers. Neither responding nor refractory patients developed sepsis during this treatment.

Conclusions: Chemotherapy is safe and effective treatment for patients with infected malignant breast ulcers and does not cause systemic sepsis.

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KEY WORDS: **locally advanced breast cancer; tumor infection; T4b breast cancer; Stage IIIB breast cancer; neoadjuvant chemotherapy**

INTRODUCTION

Because distant metastases from breast cancer often do not become clinically apparent until late in the course of the disease, and the breast itself is not a vital organ, untreated breast cancers may become very large, invade the skin, undergo necrosis, and form large ulcers that penetrate to the chest wall. Such ulcers, are the classic manifestation of breast cancer [1], and remain common in populations with limited access to medical care. The ulcers sometimes cause severe bleeding and are often purulent, although systemic sepsis is rare.

In 1982 a program of neoadjuvant cyclophosphamide, Adriamycin, and 5-fluorouracil (CAF) for patients with locally advanced breast cancer (stage IIIA and B) was initiated at the Kings County Hospital Center Breast Clinic [2]. Patients presenting with both T4 breast tumors and distant metastases also received CAF as their primary treatment. There was concern that chemotherapy-induced granulocytopenia and immunosuppression might precipitate systemic sepsis in patients with infected ulcers. This retrospective analysis was performed to determine whether chemotherapy, as the sole initial treatment of patients with skin ulceration, was sufficient to induce tumor regression and ulcer healing, and whether sepsis occurred during treatment.

PATIENTS AND METHODS

Of 38 patients with ulcerated breast tumors who received primary chemotherapy from 1982 to 1996, five were lost to follow-up after the first course, so that 33

*Correspondence to: Albert S. Braverman, M.D., Division of Hematology-Oncology, Department of Medicine, Health Sciences Center at Brooklyn, State University of New York, Box 55, 450 Clarkson Avenue, Brooklyn, NY 11203-2089. Telephone: 718-270-2559; Fax: 718-270-1544.

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were evaluable for this study; their charts were retrospectively reviewed.

Courses of 600 mg/M^2 cyclophosphamide and 5-fluorouracil, and 40 mg/M^2 Adriamycin were administered intravenously every 3 weeks; methotrexate 40 mg/M^2 was substituted for Adriamycin (CMF) in patients with preexisting cardiac disease. Doses were reduced by 10–25% in patients >70 years of age, depending on performance status. When the absolute neutrophile count was <1,500/mm^3 21 days after the last course of chemotherapy, treatment was delayed until the neutrophile count exceeded this level, but doses were not reduced. The delay was not >2 weeks. We do not use G- or GM-CSFs to reduce the duration of granulocytopenia in afebrile patients receiving these regimens. Ulcers were irrigated and dressed daily, but patients were not treated with antibiotics before or during primary chemotherapy.

Patients were examined for primary tumor response, and for ulcer response, 3 weeks after the second course of chemotherapy. Tumor response parameters were complete disappearance of the palpable tumor mass (complete response) or decrease in its size by >50% of the product of its two greatest diameters (partial response). Follow-up mammography was used to confirm tumor regression when the results of physical examination were ambiguous. Complete ulcer response was defined as reepithelialization of the entire ulcerated area; partial ulcer response was defined as >50% epithelialization. In stage IV patients, response parameters also included alleviation of bone pain and objective regression of other metastases, when present.

Mastectomy was routinely performed on all stage IIIB patients with technically resectable tumors after two to four-courses of chemotherapy. Primary chemotherapy was continued in responsive stage IV patients until relapse.

RESULTS

Thirty-three evaluable patients with malignant breast ulcers received chemotherapy as their first treatment: CAF in 28 patients and CMF in 5 patients. Their mean age was 53 years, median 55.5 years, with a range of 26–84 years. Twenty patients were stage IIIB, and 13 patients stage IV.

Eleven patients had ulcers that involved <50% of the breast and did not reach the chest wall. In 22 patients, the ulcers involved >50% of the breast or penetrated to the chest wall; 13/33 had >50% involvement of the breast by the ulcer, in 16/33 the ulcer penetrated to the chest wall, and in 7/33 both conditions were present.

Partial or complete remission of the primary tumor invariably resulted in ulcer healing, and no ulcer healed without >50% tumor regression. Complete ulcer healing occurred in 18/33 patients, and partial healing in 3/33, for a 64% total response rate. Of 28 patients treated with CAF, 20 responded, and 1/5 treated with CMF responded. Of 13 patients whose ulcers involved >50% of the breast, 7 healed completely and 2 healed partially. Of 16 patients whose ulcers penetrated to the chest wall, 8 healed completely and 2 healed partially (see Table I).

TABLE I. Response of Breast Ulcers to Primary Chemotherapy*

	n	CR n (%)	PR n (%)	NR n (%)
Ulcerated breast tumors	33	18(55)	3(9.1)	12(36)
Subsets				
Ulcer <50% of breast and movable	11	7(64)	0	4(36)
Ulcer >50% of breast[a]	13	7(54)	2(15)	4(31)
Chest wall penetration[a]	16	8(50)	2(13)	6(38)

*CR, complete remission, complete reepithelialization of the ulcer; PR, partial remission, complete reepithelialization of the ulcer; NR, no response, <50% reepithelialization of the ulcer.
[a]The ulcers of seven patients involved >50% of the breast *and* were fixed posteriorly.

Despite the gross purulence of most of the ulcers, no patient was septic at presentation and none developed sepsis during chemotherapy, although the purulent ulcers persisted in nonresponders. Because patients received most of their chemotherapy as outpatients, we cannot exclude fever at some point during their treatment, but temperatures >100°F were not recorded at the time of their clinic visits. No patient required antibiotics during treatment. Low grade temperature elevations in patients with very large ulcers may be due to inflammation rather than systemic infection. Absolute neutrophile counts <1,200/mm^3 are uncommon with the chemotherapeutic regimens used in this study, and did not occur in any of the patients reported here. Elderly patients are at increased risk for severe leukopenia during chemotherapy, but only 5 of the 33 patients we treated were >70 years of age. Perhaps because of the lower doses these patients received, none had a neutrophile nadir of <1,200 during treatment.

After two- to four-courses of chemotherapy, 13/20 stage IIIB patients had mastectomies, followed by radiation therapy. Median and mean relapse-free survival duration for the 33 patients were 10.5 and 23 months. Median and mean overall survival times were 13.5 and 27 months. Nineteen patients died from metastatic breast cancer after a median of 12 and a mean of 21 months; 11 are alive and relapse-free at a median of 17.5 and a mean of 36 months since initiation of primary chemotherapy. The remaining three patients were lost to follow-up after the completion of systemic and local therapy.

Seven patients, whose ulcers responded to primary

chemotherapy, received no subsequent local treatment because of distant metastases, and were therefore evaluable for healing durability. All had ulcers involving >50% of the breast and/or penetrating to the chest wall before treatment. The median and mean duration of relapse-free survival were 4.5 and 8.1 months (range, 3–20 months), respectively. Relapse of local and distant disease was synchronous, but recurrent ulcers were never as extensive as they had been at presentation.

DISCUSSION

A MEDLINE literature search, 1966–1996, revealed only a single case report of the response of a breast ulcer to primary chemoendocrine therapy [3], although the ability of neoadjuvant chemotherapy to induce remissions of stage IIIB breast tumors is well-documented [2,4–7], and it is now standard treatment for most patients with stage IIIB breast cancer. Chemotherapy is also the treatment of choice for many of those presenting with stage IV disease. Although the standard chemotherapeutic regimens, such a CAF, do not often cause severe granulocytopenia, they usually lower the white blood count and may cause transient immunosuppression.

Because of the fear of resulting sepsis, radiation has been the initial therapy of some patients with infected malignant ulcers. Our data suggest that chemotherapy is safe in these patients and can completely heal even the largest ulcers in many. The absence of systemic sepsis before or during treatment is probably due to the poor blood supply of ulcerated breast tumors, which may be responsible for their development. We do not know whether patients with infected breast ulcers will tolerate dose-intensive cytotoxic therapy, which always causes severe granulocytopenia, as well as the patients reported here. Conventional neoadjuvant chemotherapy may be used initially to attempt to achieve healing before dose-intensive therapy is initiated.

Our data suggest that systemic chemotherapy alone is a safe and effective initial treatment for many patients with malignant breast ulcers.

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